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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 09/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,867	GODDARD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/31/05; 7/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 May 2005 has been entered.

2. Claims 1-41 have been canceled.

Claims 52-55 have been added.

3. Claims 42-55 are pending and under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Response to Arguments

6. The rejection of claims 42-51 and applied to newly added claims 52-55 under 35 U.S.C 101 because the claimed invention is not supported by a substantial asserted utility or a well-established utility is maintained.

The response filed 5/31/2005 has been carefully considered, but is deemed not to be persuasive. Applicant reviews the evidentiary standard regarding the legal presumption of utility. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Applicant argues that the utility need not be proved to a statistical certainty, a reasonable correlation between the

evidence and the asserted utility is sufficient and applicant cites numerous case law in support of applicants arguments that for a therapeutic and diagnostic use, utility does not have to be established to an absolute certainty and the evidence need not be direct evidence so long as there is a reasonable correlation between the evidence and the asserted utility. Applicant argues that as set forth in MPEP 2107 II(B)(1) "If applicant has asserted that the claimed invention is useful for any particular practical purpose... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." In response to these arguments, the examiner agrees with Applicant's statement that absolute certainty is not the legal standard for utility. However, the rejection does not question the presumption of truth, or credibility, of the asserted utility. The asserted utilities of cancer diagnostics and cancer therapeutics for the claimed polypeptides are credible and specific, however, they are not substantial. The data set forth in the specification are preliminary at best because the specification does not teach the expression of the PRO180 polypeptide nor any particular biological activity or function of the polypeptide. Applicant summarizes their arguments and the disputed issues involved (beginning at page 10 of the response). Applicant reiterates that Example 18 in the specification shows that mRNA encoding the PRO1069 polypeptide is more highly expressed in normal lung compared to lung tumor more highly expressed in rectal tumor compared to normal rectum and applicant asserts that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein and based on the identification of the mRNA encoding the PRO180

polypeptide over-expressed in normal lung and rectal tumor relative to lung tumor and normal rectum, respectively, renders the PRO180 polypeptide useful as a diagnostic tool for the determination of the presence or absence of tumor according to applicant. In support, applicant again argues with the declaration of J. Christopher Grimaldi (previously submitted in the response filed 2/2/04), which states that the expression of mRNA and the encoded protein are highly correlated and the references provided therein support this. This has been fully considered, but is not found persuasive. First, it is important to note that the instant specification provides no information regarding PRO180 polypeptide levels in tumor samples relative to normal samples. Only gene expression data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 42-55 based upon 35 U.S.C. 101 and 112, first paragraph, since it is limited to a discussion of data regarding the gene expression of the PRO180 cDNA and not gene expression levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. There is no evidentiary support to Dr. Grimaldi's statement that if a difference in gene expression is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al (Journal of Proteome Research 2:405-412, 2003, Ids reference 21 filed 5/31/2005) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression

level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicant argues that they have established that the accepted understanding in the art is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein and applicant argues with the previously submitted second declaration of J. Christopher Grimaldi (previously submitted in the response filed 2/2/04), which states that those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed ...the gene product or polypeptide will also be over-expressed and this same principle applies to gene under-expression. Further, applicant argues with the declaration of Dr. Paul Polakis (previously submitted 7/9/04) which states that based upon his experience accumulated in more than 20 years of research, that it is his scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase of the encoded protein in the tumor cell relative to the normal cell and that based on his experience although reports exist where such a correlation does not exist, such reports are exceptions to a commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein and applicant cites

Alberts [a] (4th ed. 2002; previously submitted on 12/13/04), Alberts [b] (3rd ed. 1994; submitted herewith as Exhibit 1), Lewin (cited on PTO-892 mailed 4/9/04) and Zhigang (Ids reference 29, filed 5/31/05) for support that mRNA expression correlates with protein expression. The declarations of Dr. Grimaldi and Dr. Polakis and applicant's arguments have been fully considered, but are not found persuasive. Alberts [b] and Lewin actually support the fact that further research would have to be carried out to determine if the polypeptide expression levels track with the expression levels of the corresponding mRNA. Alberts [b] and Lewin show that there are several levels that control gene expression both at the transcriptional (i.e., mRNA synthesis) and the translational (i.e., protein production) levels. Thus, one skilled in the art would not simply accept that increased mRNA levels directly correlate with the level of the corresponding polypeptide in view of the multitude of controls at the transcriptional and translational levels. With respect to applicant's arguments regarding the art of Zhigang et al, the art of Zhigang et al does show protein expression, however, the experiments were carried out to demonstrate this and as such Zhigang support that one needs to actually determine the expression of the protein to be sure of expression. Applicant also argues that Alberts [a] (4th ed. 2002). figure 6-3 on page 302 illustrates the general principle that there is a correlation between increased gene expression and increased protein expression. In response to this argument, while increased transcript levels can lead to increased polypeptide levels, there are other regulatory factors that also effect the rate of translation as evidenced by Alberts [b] (Exhibit 1) in Figure 9-72. Additionally, Meric et al (Molecular Cancer Therapeutics, 1:971-979, 2002, Ids

reference 26, filed 5/31/2005) teaches that in addition to variations in mRNA sequences that increase or decrease translational efficiency, changes in the expression or availability of components of the translational machinery (i.e., over-expression of eIF4E, eIF4G, eIF-2α, eIF-4A1, ect...) as well as activation of translation through aberrantly activated signal transduction pathways also effect the rate of translation in cancerous cells. Figure 6-3 of Exhibit 2 (Alberts, 4th ed. 2002) does not account for these other types of controls that exist in cancerous cells, which are more directly relevant to the claims at issue. Applicant argues that Meric et al states at page 791, left column that the fundamental principle of molecular therapeutics is to exploit differences in gene expression between cancer cells and normal cells and most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription and applicant concludes that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression. First, the statements by Meric appear to have been taken out of context. Meric indicates most efforts have concentrated on gene expression at the mRNA level due to the advent of cDNA array technology, which facilitated this type of analysis. Further, Meric et al in agreement with Alberts and Lewin acknowledges that gene expression is quite complicated and is regulated at the level of mRNA stability, mRNA translation and protein stability and Meric goes on to discuss that the components of the translation machinery and signal pathways involved in the activation of translation initiation represent good targets for cancer therapy (see pages

975-976). If it is the accepted understanding in the art that there is a direct correlation between mRNA levels and the level of expression of the encoded polypeptide, there would not be a need to target the translational machinery, unless of course the two are regulated separately.

Applicant argues the Chen et al reference, stating that Chen reports that 21.4% of the genes showed a statistically significant correlation between protein and mRNA expression. Contrary to applicant's assertion that Chen provides scant evidence to counter applicant's asserted utility, a percentage of 21.4%, much lower than 50% would not indicate that it is the norm rather than the exception that protein levels correlate with mRNA expression. Given the lack of a significant correlation (i.e., greater than 50%) as shown by Chen et al one of skill in the art would not find that there is a general correlation between changes in mRNA level and changes in protein level. Applicant also argues that Chen did not distinguish between cancer and normal samples in their analysis. It is unclear what this argument has to do with the present utility rejection, because applicant's asserted utility is based on the assertion that mRNA over-expression will lead to an over-expression of the encoded polypeptide within the same cells. By comparing mRNA and protein expression levels within the same tumor samples, Chen et al found that only 17% of the protein spots show a statistically significant correlation between mRNA and protein and the expression of individual isoforms of the same protein may or may not correlate with the mRNA, indicating that separate and likely post-translational mechanisms account for the regulation of isoform abundance. Further, Chen et al states "The use of mRNA expression patterns by

themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of a protein present in a given cell or tissue." (see page 304, right column). Clearly, Chen et al would not agree with applicant's assertion that substantial changes in mRNA levels will correspond to substantial changes in polypeptide expression in view of the distinct regulatory factors of both transcription and translation. Applicant's arguments do not fully take into consideration these distinct regulatory mechanisms, which are present in biological cells as evidenced by the art.

The art of Lewin, Zhigang, Alberts [a], Alberts [b], Meric and Chen et al are all examples of post-transcriptional regulation of protein levels, they are not inconsistent with applicant's position that mRNA levels correlate, more often than not, with protein levels. In response to this argument, Gygi et al (Molecular and Cellular Biology, 19(3):1720-1730, March 1999, Ids reference 19 filed 5/31/2005) states "We found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold." (see abstract). Also, Haynes et al (1998, Electrophoresis 19:1862-1871, Ids reference 20 filed 5/31/2005), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript

level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes et al concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). More recently, and in agreement with Gygi and Haynes, Hanish S. [a] (Nature Reviews, Applied Proteomics Collection, pp. 9-14, March 2005, Ids reference 2 filed 7/1/05) recently stated "There is a need to profile gene expression at the level of the proteome and to correlate changes in gene-expression profiles with changes in proteomic profiles. The two are not always linked-numerous alterations occur in protein levels that are not reflected at the RNA level." (see page 12). Further, Hanash [a] teaches that tumors are complex biological systems and no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics (see abstract). Hanash et al [b] (The Pharmacogenomics Journal, 3(6):308-311, 2003, Ids reference 1 filed 7/1/05) states "However perfected DNA microarrays and their analytical tools become for disease profiling, they will not eliminate a pressing need for other types of profiling technologies that go beyond measuring RNA levels, particularly for disease-related investigations." (see page 311). According to Hanash et al [b], there is a need to assay protein levels and activities and numerous alterations may occur in proteins that are not reflected in changes at the RNA level (see page 311). Clearly, contrary to applicant's arguments and as evidenced by the art above, it is not established in the art that the accepted understanding or "general rule" is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. The literature

supports that RNA expression cannot inevitably be correlated with levels of the encoded polypeptide and one skilled in the art would not assume that the levels of RNA are predictive of the levels of the encoded polypeptide given the distinct regulation of transcription and translation as evidenced by Alberts, Lewin, Meric, Gygi et al, Haynes et al, Hanash S [a] and Hanash et al [b]. One skilled in the art would do further research to determine whether or not the PRO180 polypeptide was over-expressed in normal lung and rectum tumor relative to lung tumor and normal rectum, respectively. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. This situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct, 1966), in which the court held that

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "[i]t is not a reward for the search, but compensation for its successful conclusion."

For these reasons the rejection is maintained.

7. The rejection of claims 42-51 and newly added claims 52-55 under 35 U.S.C. 112, first paragraph, is maintained. Specifically, since the claimed invention is not supported by a substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

8. The rejection of claims 42-43 and newly added claims 52-55 under 35 U.S.C 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention is maintained.

The response filed 5/31/2005 has been carefully considered, but is deemed not to be persuasive. Applicant reviews the evidentiary standard regarding the legal presumption of written description. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of written description. The response argues that the claims have been amended to recite that the claimed polypeptides have at least 95% amino acid sequence identity to several polypeptides related to SEQ ID NO:2 and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:2 in rectal and lung tissue samples." Applicant argues that the instant claims are analogous to the claims discussed in Example 14 of the written description training materials, in which written description was found to be satisfied for claims relating to polypeptides having 95%

homology to a particular sequence and possessing a particular activity, even though applicant had not made any variants. In response to this argument, unlike example 14, which encompasses a genus of molecules having significant structural similarity and identical biological functions, which distinguishes members of the genus from those excluded, the presently claimed polypeptides have not been associated with any particular biological activity or function coupled with the disclosed structure of the present claims and the encompassed polypeptides may have functions and structures that differ greatly from that of PRO180, particularly in the case where the polypeptide has 95% or 99% amino acid sequence identity with the extracellular domain of SEQ ID NO:2, which is an extremely broad genus of polypeptides. There is no functional limitation with respect to these partial structures of SEQ ID NO:2 and as above, the encompassed polypeptides may have substantially different structures and biological functions. This is not similar to example 14 of the written description training materials, which is drawn to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, which distinguishes members of the genus by both structure and function. The only distinguishing characteristic of the present claims is sequence identity or partial sequence identity in the case of "the extracellular domain". Therefore, one of skill in the art would not be able to identify the encompassed molecules as being identical to those instantly claimed. Further, the specification does not disclose any polypeptide that is 95% or 99% identical to SEQ ID NO:2 and is over-expressed in rectum tumor and normal lung relative to normal rectum and lung tumor respectively. Conception does not occur unless one has a mental

picture of the structure of the molecule, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.

Applicant remarks the PTO has issued many patents containing claims to variant sequences where applicants did not actually make such nucleic acids or proteins. In response to this argument the examiner does not know the prosecution history of these cases and will not comment on the prosecution history of these cases.

9. The rejection of claims 42-43, 50-51 and applied to newly added claims 52-55 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 5/31/2005 has been carefully considered, but is deemed not to be persuasive. The response argues as above for the that it is well established in the art how to make the claimed polypeptides which have at least 95% amino acid sequence identity to SEQ ID NO:2 and applicants have disclosed how to determine if the claimed polypeptides or encoding polynucleotides are differentially expressed in rectal tumors or normal lung compared to normal rectum or lung tumor and applicant argues as above that one of skill in the art would believe that it is more likely than not that the PRO180 gene and polypeptide are differentially expressed in rectal and lung tumor such that they can be used as a cancer diagnostic. In response to these

arguments, as discussed above the art underscores the unpredictability in the art and evince that the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation as discussed above (also see the art of Fu et al, Powell et al, Vallejo et al, Jang et al and Pennica et al, all cited in the Office Action mailed 9/4/03).

With respect to the protein variants encompassed by the claims, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein variants that are 95% or 99% identical to SEQ ID NO:2 much less variants that are 95% or 99% identical to the extracellular domain of SEQ ID NO:2 in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments. The specification does not disclose any polypeptide variant that is at least 95% identical to SEQ ID NO:2 and is differentially expressed in rectal and lung tumors and one of skill in the art would not know if such a polypeptide even exists. Further, the specification does not teach a single biological function of the claimed polypeptide of SEQ ID NO:2 and one of skill in the art would not know how to use the claimed polypeptide variants or screen for the same. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai

Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

Due to the large quantity of experimentation necessary to generate the indefinite number of protein variants recited in the claims and possibly screen same for some activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art (Burgess et al, Lazar et al, Schwartz et al and Lin et al, all previously cited in the Office Action mailed 9/4/03) which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

New Grounds of Rejections

10. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 21, line 13. Applicant is required to check the entire disclosure and delete all the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01

11. Claims 42-44, 46-48 and 50-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 42-44, 47-48 and 50-55 comprise the limitations that the claimed protein lacks its associated signal peptide or comprises an "extracellular domain" optionally lacking its associated signal peptide. These limitations are indefinite because neither the figure (figure 2) nor the specification define or teach the metes and bounds of the extracellular domain(s). Figure 2 indicates that the polypeptide of SEQ ID NO:2 contains multiple transmembrane domains and thus, is expected to have more than one extracellular domain and it is unclear which of these is "the extracellular domain" referred to in the claims. The recitation that "the extracellular domain" is amino acids 34-366 of SEQ ID NO:2 is indefinite because the polypeptide of SEQ ID NO:2 is only 266 amino acids in length and amino acids that are part of a transmembrane domain would not also be part of "the extracellular domain" (see Figure 2). Further, the recitation that the "extracellular domain"..."lacking its associated signal sequence" is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of protein production in the cell. It is noted that Figure 2 provides no written description of the extracellular domain(s). As such, the metes and bounds of the now claimed fragments cannot be ascertained.

b. Claims 42-44, 46, 48 and 50-55 are indefinite in the recitation of a "signal peptide" in claims 42-44, 46, 48 and 52-53 because neither Figure 2 nor the specification indicate that the polypeptide actually comprises a "signal peptide" and one of skill in the art would not be reasonably apprised of the metes and bounds of the "signal peptide" of the instant claims.

12. Claims 42-44, 47-48 and 50-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed had possession of the claimed invention. This is a NEW MATTER rejection.

The amendments to the claims filed 12/13/04 and 5/31/05 (newly added claims 52-55) have introduced NEW MATTER into the claims. Claims 42-44 were amended in the response filed 12/13/04 to recite that the claimed polypeptides are more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively and wherein the extracellular domain is amino acids 34-366 of SEQ ID NO:2. The response filed 12/13/2004 pointed to Figure 2 and Example 18 of the as-filed specification. The disclosure as pointed to by applicant does not provide adequate written support for the limitations of the present claims. Figure 2 as-filed does not disclose the extracellular domain as being amino acids 34-366 of SEQ ID NO:2. In fact SEQ ID NO:2 is only 266 amino acids in length and the region spanning amino acids 34-266 (assuming 266 is correct) would encompass several transmembrane domains that would not also be part of the extracellular domain(s). Figure 2 lacks adequate written support for an extracellular domain that is amino acids 34-366 of SEQ ID NO:2. Additionally, the specification as originally filed does not disclose any nucleic

acid or encoded polypeptide that is at least 95% identical to SEQ ID NO:2 or portions thereof (i.e., lacking the signal peptide or "the extracellular domain") that is over-expressed in rectum tumor or normal lung relative to normal rectum and lung tumor respectively. The only polynucleotide that is disclosed to be over-expressed in rectum tumor or normal lung relative to normal rectum and lung tumor respectively is the nucleic acid of DNA26843-1389 and this nucleic acid only encodes the polypeptide of SEQ ID NO:2 (see example 18). There is no disclosure of any PRO180 polypeptide that is over-expressed in rectum tumor or normal lung relative to normal rectum and lung tumor respectively, as presently claimed. Thus, the disclosure does not provide adequate written support for polypeptides that are at least 95% identical SEQ ID NO:2 or portions thereof (i.e., lacking the signal peptide and "the extracellular domain") that are over-expressed in rectum tumor or normal lung relative to normal rectum and lung tumor respectively or polynucleotides that encode said polypeptides. Thus, the claims now recites limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the present claims in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

Priority

Applicant claims priority to five previous applications in the amendment of 09 July 2004. Priority is granted to PCT/US00/23328, filed 24 August 2000, as the disclosure of '328 is identical to the instant disclosure. However, priority is not granted to USSN PCT/US00/08439, 09/380,137, PCT/US99/12252 and 60/096,012 since these applications do not disclose the gene amplification assay (Example 18) upon which applicant relies for utility of the instantly claimed polypeptides. Therefore, the filing date for the purpose of art rejections is deemed to be 24 August 2000. Applicant is reminded that benefit to a prior-filed application requires written description and enablement under the first paragraph of 35 U.S.C. 112.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 42-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Feng et al (WO 99/24836, published 5/99, cited previously on PTO-892 mailed 9/4/03).

As discussed above, the filing date for the purpose of art rejections is deemed to be 24 August 2000, thus, the Feng reference is being re-applied because the priority

applications do not disclose the gene amplification assay (Example 18) upon which applicant relies for utility of the instantly claimed polypeptides.

The claims recite an isolated polypeptide having at least 95% amino acid sequence identity to a polypeptide of SEQ ID NO:2 and fused to a heterologous polypeptide, which is a tag polypeptide or an Fc region of an imunoglobulin.

Feng et al teach a polypeptide (SEQ ID NO:144) that is 100% identical to SEQ ID NO:2 and the polypeptide can be fused to an epitope tag (see page 211). With respect to the differential expression of the polypeptide of SEQ ID NO:2 in rectum and lung tumors, Applicant is reminded that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Further, the intended use of the polypeptide to generate an antibody, which can be used to detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue, is given no patentable weight (MPEP 2111.02).

15. Claims 42-55 are rejected under 35 U.S.C. 102(a) as being anticipated by Baker et al (WO 99/63088, published 12/99, cited previously on PTO-892 mailed 9/4/03).

As discussed above, the filing date for the purpose of art rejections is deemed to be 24 August 2000, thus, the Baker et al reference is being re-applied because the priority applications do not disclose the gene amplification assay (Example 18) upon which applicant relies for utility of the instantly claimed polypeptides

Claims 42-55 have been described supra.

Baker et al teach SEQ ID NO:2 and the polypeptide can have an epitope tag or an Fc region (see page 50, Figure 15 and page 310). With respect to the differential expression of the polypeptide of SEQ ID NO:2 in rectum and lung tumors, Applicant is reminded that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Further, the intended use of the polypeptide to generate an antibody, which can be used to detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue, is given no patentable weight (MPEP 2111.02).

Conclusions

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature, matching or

filed papers or relating to the status of this application or proceeding should be directed to Tony Parks for Art Unit 1643 whose telephone number is 571-272-0543.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER